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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/187,669	11/05/1998	EDUARDO MARBAN	47728	3339

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/187,669	MARBAN, EDUARDO	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 7/29/2004, in which several claims were amended (claims 32, 37 & 46) and in which several new claims were added (claims 47-64). Claims 32-64 are pending and under consideration in the instant application.

Any grounds of rejection in the previous office action, mailed 1/29/2004, not addressed herein are withdrawn. This action is not final as there are new grounds of rejection presented herein that were not necessitated by applicant's amendment of the claims in the response filed 7/29/2004.

Double Patenting

Claims 37-42 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 32-36. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 37-42 comprise the same methods steps as claims 32-36. The fact that the preamble and stated outcome of the claims are different does not obviate the fact that the same method is being claimed in each case. **This objection is maintained for the reasons of record in the office action mailed 1/29/2004 and which are repeated above.**

Response to Arguments/Double Patenting Objection

Applicant's arguments filed 7/29/2004 have been fully considered but they are not persuasive. The response essentially argues that it is sufficient to have a difference in the intended outcome of different claims to distinguish between the claims, even without any

positive action step in the claims that distinguishes the claims. The response argues that although the different methods may have common methods steps, they are different in scope and substantive content because they are directed to different aspects of the invention, and thus, they are not substantial duplicates of one another.

These arguments are not persuasive in that there is no difference in the positive action steps recited in the claims. Each claim differs from the other only in the intended outcome as recited in the preamble and in a declarative statement that, having practiced the exact same methods steps, one either predicts the pharmacological effect of a drug candidate compound on a tissue that expresses a particular protein or one identifies a protein as a potential drug target protein. As the claims are currently written, practicing the exact same methods steps necessarily results in accomplishing both of the recited outcomes. Given these facts, claims 37-42 must be considered as substantial duplicates of claims 32-36.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new rejection.

Claim 32 recites the following limitation, "...wherein a difference in phenotype between the host cells in which expression of the protein has been modulated and the phenotype of control cells in which expression of the protein has not been modulated predicts the pharmacological effect of a drug candidate compound would have in a cell, tissue or organ that expresses the protein..." (examiner's emphasis added). Claim 37 recites the following limitation, "...wherein a difference in phenotype between the host cells in which expression of the protein has been modulated and the phenotype of control cells in which expression of the protein has not been modulated identifies the protein as a potential drug target protein..." (examiner's emphasis added). There is no literal or inherent support in the originally filed claims or specification for either of these declarative statements wherein a difference in phenotype upon expression of literally any protein necessarily (i) predicts the pharmacological effect of a drug candidate compound would have in a cell, tissue or organ that expresses the protein, or (ii) identifies the protein as a potential drug target protein. In submitting new claims 32 and 37 in the response filed 11/6/2003, applicant indicated that such support was found, for example, in Example 2 of the instant specification. This is not accurate. The mere fact that applicant might have followed the general outline of the method recited in the rejected claims in one particular experiment for a given protein does not provide support for the broadly claimed method recited in the rejected claims. Therefore, the cited declarative statements are impermissible NEW MATTER.

Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in

the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicant's amendment of the claims in the response filed 7/29/2004.**

Amended claim 46 recites the term "traditional drug discovery strategy". There is no literal or inherent support for this term in the originally filed specification. Therefore, this term is impermissible NEW MATTER.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 32-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is directed to a method for predicting the pharmacological effect a drug candidate compound would have in a cell, tissue or organ that expresses a given protein wherein the expression level of the protein is modulated and a difference in phenotype between the test cells and suitable control cells is observed. The claim recites that observation of such a difference necessarily indicates the pharmacological effect of a candidate drug compound. Claim 37 is directed to a method of identifying a protein as a potential drug target protein and comprises the exact same methods steps as claim 32. Claim 32 recites that observation of a difference in phenotype for test cells compared to control cells means the protein whose expression has been modulated has been identified as a potential drug target. Because the

preamble and conclusions for the two claims are different while the methods steps are the same, it is unclear what additional steps, if any, are required to achieve the stated outcome for each claim. **This rejection is maintained for the reasons of record in the office action mailed 1/29/2004 and which are repeated above.**

Claim 46 provides for the use of a potential drug target protein in a "traditional" drug screening strategy. The term "traditional" is subjective and open to interpretation in the absence of an explicit definition in the originally filed specification. No such definition is provided. It would be remedial to amend the claim to include the limitations intended by the subjective term, "traditional".

Response to Arguments/112 2nd Rejection of Claims 32 & 37

Applicant's arguments filed in the response of 7/29/2004 have been fully considered but they are not persuasive. The response essentially argues the skilled artisan would understand that the recited methods of claims 32 and 37 are directed to different aspects of the invention, and both methods would be evident to the skilled artisan based upon applicant's disclosure.

These arguments are not persuasive in that there is no difference in the positive action steps recited in the claims. Each claim differs from the other only in the intended outcome as recited in the preamble and in a declarative statement that, having practiced the exact same methods steps, one either predicts the pharmacological effect of a drug candidate compound on a tissue that expresses a particular protein or one identifies a protein as a potential drug target protein. As the claims are currently written, practicing the exact same methods steps necessarily results in accomplishing both of the recited outcomes. It appears applicant is trying to distinguish the two sets of claims based solely upon some undefined set of thought processes that

are not clearly delineated in the instant specification. Contrary to applicant's assertion, the instant specification does not clearly indicate what additional positive action steps are required, if any, in order to obtain the different outcomes using the currently recited methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 32-46, 52-55, 59, 63 & 64 are rejected under 35 U.S.C. 102(e) as being anticipated by Kamb (U.S. Patent No. 5,955,275; see the entire patent). **This rejection is maintained for the reasons of record in the office action mailed 1/29/2004 and which are repeated below.**

Kamb teaches methods for identifying nucleic acid sequences that affect a cellular phenotype. The methods use a reporter gene whose level of expression correlates with the phenotype. An expression library is introduced into the cells and those cells exhibiting changes in reporter expression level are selected (e.g. Abstract). The expression library of the invention preferably expresses sequences encoding protein fragments, peptides or proteins that are termed "perturbagens" (column 3, lines 0-26). Host cells of the invention can be of several types, including human cells isolated from tissues and cancers (e.g. melanoma, colon cancer, etc.). Following expression, cells are selected based upon the decrease or increase in expression of the

reporter protein (which can be considered a "target" polypeptide) upon expression of the library members (e.g. column 3, lines 20-26). The patent describes "perturbagens" as molecules that act in a transdominant mode to interfere with the function of endogenous cellular components. Perturbagens are typically proteinacious but may also be nucleic acids (e.g. antisense). Thus, the perturbagens of the patent can be considered "selected" or "target" proteins. Kamb teaches that one manner in which perturbagens can exert their effect is by forming a binding complex between the wildtype target polypeptide and a perturbagen that is a fragment of the wildtype protein. Such a binding complex, comprising an altered form of the wildtype protein with the wildtype protein, is expected to behave in a manner similar to a small molecule inhibitor of the wildtype protein (e.g. Figures 1A-1C; columns 4-5, bridging paragraph). A perturbagen functioning in such a manner and selected for its ability to increase or decrease the expression of a reporter protein would necessarily be selected based upon its ability to "mimic" or "predict" the effect a drug compound. A perturbagen functioning in this manner would also necessarily constitute a "dominant negative" effect as defined in the specification (e.g. pages 12-13 of the instant specification-bridging paragraph). Kamb teaches that the perturbagen targets proteins are as interesting as the perturbagens themselves and can be readily identified by standard techniques (e.g. two-hybrid technologies) (e.g. column 15, lines 11-40).

Response to Arguments/Kamb Rejection

Applicant's arguments filed in the response of 7/29/2004 have been fully considered but they are not persuasive. In the response, applicant has amended the claims to recite specific phenotypes such as cell growth, blebbing, change in electrical charge, etc. The response essentially argues that since the teachings of Kamb et al are directed explicitly to the use of a

reporter gene whose expression is affected by the "perturbagen" of his invention, the teachings of Kamb et al do not encompass the amended claims.

Kamb teaches that the reporter gene used in his methods is one that reflects the phenotypic state of a particular cell (column 3, lines 5-10). The reporter may be an endogenous gene, preferably encoding a cell surface marker or it may be a foreign gene placed under the control of a cell-type-specific or cell-state-specific promoter. The reporter is expressed in host cells at a level sufficient to permit its rapid and quantitative analysis (column 3, lines 29-37). Kamb teaches his invention can be used to generate a perturbagen disruption that causes a phenotypic transformation such that the original cell type is converted into a different cell type I which the reporter gene is not expressed (e.g. cell differentiation as observable phenotype; column 4, lines 25-33). Kamb teaches several different types of reporters, including cell surface markers (e.g. CD20), antibiotic resistance markers (e.g. as a "growth/no growth" phenotype) and enzymatic proteins (e.g. green or blue fluorescent proteins; column 5, lines 4-10; column 7, lines 12-25). Importantly, Kamb teaches that a reporter comprises any gene product for which screens or selections can be applied (column 8, lines 33-67). Clearly, the markers taught by Kamb et al encompass phenotypes as recited in the amended claims. For example, selection assays for the expression of an antibiotic resistance marker would necessarily be based upon a "growth" phenotype. Alternatively, the use of enzymatic markers such as GFP or neomycin resistance marker would demonstrate changes in transcriptional, translational, enzymatic catalysis and functional modification of the host cell expressing GFP as compared to a cell not expressing GFP.

Claims 32-34, 36-38, 44, 47, 55, 61 & 64 are rejected under 35 U.S.C. 102(b) as being anticipated by Marshall et al (Neuron, Vol. 14, pages 211-215, 1995; see the entire reference). **This is a new rejection.**

Marshall et al teach the construction and characterization of a nucleic acid construct comprising a sequence encoding green fluorescence protein (GFP) operatively linked to a sequence encoding the NMDAR1 ion channel (e.g. Abstract). The Marshall et al reference teaches that co-expression of the NMDAR1-GFP chimera along with other NMDAR subunits in HEK293 cells results in the formation of functional ion channels having functional properties regarding voltage potentials and current across the membrane of cells expressing the proteins (e.g. Figures 2-4; page 214, column 1). The reference specifically teaches that the chimeric subunit is capable of forming hetero-oligomeric receptor complexes and that these complexes exhibit both macroscopic and unitary properties that are indistinguishable from the corresponding properties of hetero-oligomers comprising NMDAR1. The inventors contemplate the use of their chimeras to visualize the receptor subunit in transfected cell lines or primary neurons in order to address questions related to subunit assembly and clustering, and with regard to targeting of subunits to specific membrane compartments (e.g. page 214, column 1). Thus, Marshall et al teach experiments wherein the expression of the chimeric receptor directly resulted in observable phenotypes regarding electrical signaling, changes in electrical charge, transcription, translation and functional modification of the cell.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 32-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (U.S. Patent No. 5,955,275; see the entire patent) alone, or over Kamb in view of Marshall et al (reference CM on applicant's submission; Neuron, Vol. 14, pages 211-215, 1995; see the entire reference). **This is a new rejection necessitated by applicant's amendment of the claims in the response filed on 7/29/2004.**

Kamb teaches methods for identifying nucleic acid sequences that affect a cellular phenotype. The methods use a reporter gene whose level of expression correlates with the phenotype. An expression library is introduced into the cells and those cells exhibiting changes in reporter expression level are selected (e.g. Abstract). The expression library of the invention preferably expresses sequences encoding protein fragments, peptides or proteins that are termed "perturbagens" (column 3, lines 0-26). Host cells of the invention can be of several types, including human cells isolated from tissues and cancers (e.g. melanoma, colon cancer, etc.). Following expression, cells are selected based upon the decrease or increase in expression of the reporter protein (which can be considered a "target" polypeptide) upon expression of the library members (e.g. column 3, lines 20-26). The patent describes "perturbagens" as molecules that act in a transdominant mode to interfere with the function of endogenous cellular components. Perturbagens are typically proteinacious but may also be nucleic acids (e.g. antisense). Thus, the

perturbagens of the patent can be considered "selected" or "target" proteins. Kamb teaches that one manner in which perturbagens can exert their effect is by forming a binding complex between the wildtype target polypeptide and a perturbagen that is a fragment of the wildtype protein. Such a binding complex, comprising an altered form of the wildtype protein with the wildtype protein, is expected to behave in a manner similar to a small molecule inhibitor of the wildtype protein (e.g. Figures 1A-1C; columns 4-5, bridging paragraph). A perturbagen functioning in such a manner and selected for its ability to increase or decrease the expression of a reporter protein would necessarily be selected based upon its ability to "mimic" or "predict" the effect a drug compound. A perturbagen functioning in this manner would also necessarily constitute a "dominant negative" effect as defined in the specification (e.g. pages 12-13 of the instant specification-bridging paragraph). Kamb teaches that the perturbagen targets proteins are as interesting as the perturbagens themselves and can be readily identified by standard techniques (e.g. two-hybrid technologies) (e.g. column 15, lines 11-40).

Kamb teaches that the reporter gene used in his methods is one that reflects the phenotypic state of a particular cell (column 3, lines 5-10). The reporter may be an endogenous gene, preferably encoding a cell surface marker or it may be a foreign gene placed under the control of a cell-type-specific or cell-state-specific promoter. The reporter is expressed in host cells at a level sufficient to permit its rapid and quantitative analysis (column 3, lines 29-37). Kamb teaches his invention can be used to generate a perturbagen disruption that causes a phenotypic transformation such that the original cell type is converted into a different cell type I which the reporter gene is not expressed (e.g. cell differentiation as observable phenotype; column 4, lines 25-33). Kamb teaches several different types of reporters, including cell surface

markers (e.g. CD20), antibiotic resistance markers (e.g. as a "growth/no growth" phenotype) and enzymatic proteins (e.g. green or blue fluorescent proteins; column 5, lines 4-10; column 7, lines 12-25). Importantly, Kamb teaches that a reporter comprises any gene product for which screens or selections can be applied (column 8, lines 33-67).

Kamb et al does not explicitly reduce to practice some of the specific phenotypes recited in the rejected claims (e.g. differences in electrical signaling or charge, protein complex formation, etc.).

Marshall et al teach the construction and characterization of a nucleic acid construct comprising a sequence encoding green fluorescence protein (GFP) operatively linked to a sequence encoding the NMDAR1 ion channel (e.g. Abstract). The Marshall et al reference teaches that co-expression of the NMDAR1-GFP chimera along with other NMDAR subunits in HEK293 cells results in the formation of functional ion channels having functional properties regarding voltage potentials and current across the membrane of cells expressing the proteins (e.g. Figures 2-4; page 214, column 1). The reference specifically teaches that the chimeric subunit is capable of forming hetero-oligomeric receptor complexes and that these complexes exhibit both macroscopic and unitary properties that are indistinguishable from the corresponding properties of hetero-oligomers comprising NMDAR1. The inventors contemplate the use of their chimeras to visualize the receptor subunit in transfected cell lines or primary neurons in order to address questions related to subunit assembly and clustering, and with regard to targeting of subunits to specific membrane compartments (e.g. page 214, column 1). Thus, Marshall et al teach experiments wherein the expression of the chimeric receptor directly

resulted in observable phenotypes regarding electrical signaling, changes in electrical charge, transcription, translation and functional modification of the cell.

Marshall et al do not explicitly teach the use of their chimeric constructs as targets of a perturbagen (e.g. as a reporter in the sense of being modulated in response to somatic gene transfer of a nucleic acid expressing a perturbagen that increases or decreases functional activity of the NMDAR1/GFP chimera in transfected cells).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Kamb to include the chimeric ion channel receptors taught by Marshall et al because (i) Kamb teaches the use of his methods to identify and characterize nucleic acids that affect a cellular phenotype and that any reporter that comprises any gene product for which screens or selections can be used in his system, and (ii) because Marshall et al teach their chimeric constructs can be used to asses questions related to subunit assembly, functionality (e.g. changes in membrane potential) and clustering, and with regard to targeting of ion channel subunits to specific membrane compartments (i.e. protein processing). One would have been motivated to do so in order to utilize the expected benefits of the system taught by Kamb et al for identification of nucleic acid sequences that affect cellular phenotype in neuronal cell types, as suggested by Marshall et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing the reporter construct taught by Marshall et al in the methods of Kamb in order to identify nucleic acids whose expression affected different phenotypes associated with expression of the chimeric reporter (e.g. subunit assembly, functionality, cellular localization, etc.).

With regard to the other specific cellular phenotypes not specifically exemplified by the combined teachings of Kamb and Marshall et al, it would have been obvious to one of ordinary skill in the art to practice the teachings of Kamb with any protein for which screening or selection methods are known in the art because Kamb teaches that any such protein product can be used and because methods for screening for the different phenotypes (e.g. budding, blebbing, kinesis, cell death, oncogenetic transformation, etc.) are and were known in the art. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using any of the known reporter systems in conjunction with the teachings of Kamb to identify nucleic acids whose expression resulted in a change in the specifically recited phenotypes.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

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